light-emitting diodes, in which a dominant mechanism of exciton quenching involves polaron-exciton collision processes (*7*); these processes will be enhanced in the confined one-dimensional molecular wire. Precise control of polaron and exciton mobilities may overcome this problem in the future. On the positive side, polymers incorporated within the silica nanopores are less susceptible to air oxidation (*2*). From a basic science perspective, various interesting photophysical experiments using the nanoengineered polymers can be envisaged. For example, details of the difference between ultrafast photoinduced absorptions in solutions and in thin films of PPV (*8*, *9*) are yet to be understood. Further studies of the excited state absorptions in the nanoengineered PPV, especially the low-energy excited state absorption in the midinfrared region (*8*, *9*), may elucidate the differences between intra- and interchain processes in conjugated polymers. As clearly illustrated by Nguyen *et al.*, nanoengineered samples hold much promise for elucidating the photophysics of conjugated polymers and designing advanced optoelectronic devices.

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PERSPECTIVES: NEUROBIOLOGY

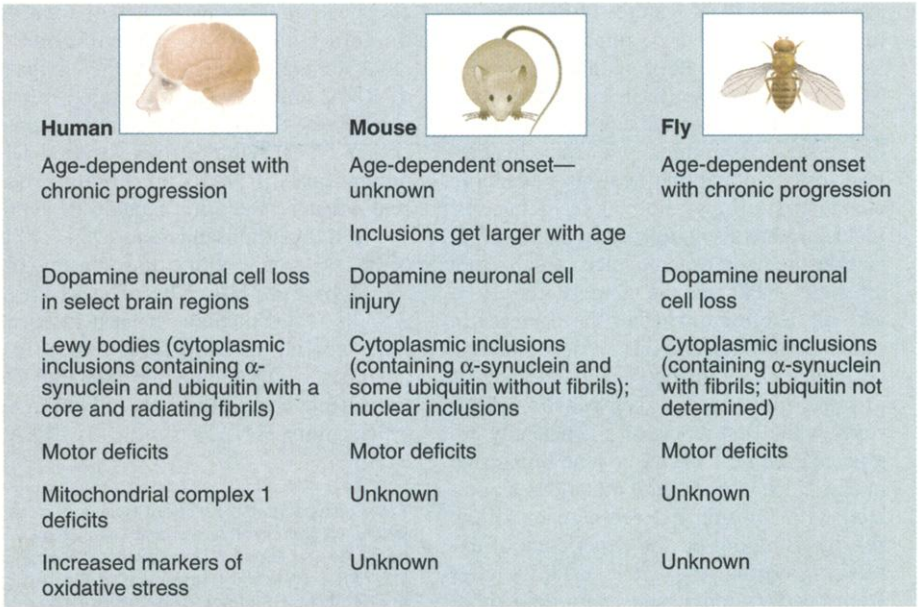
Of Flies and Mice

Valina L. Dawson

Parkinson's disease (PD) was first described 180 years ago yet the cellular mechanisms that cause a select group of dopamine neurons to die, resulting in this common neurodegenerative disorder, are unknown. Identification of mutations in the proteins α-synuclein, parkin, and the ubiquitin hydrolase UCH-L1, in patients with the rare inherited forms of PD, has yielded opportunities to understand the pathogenesis of this insidious disease through modern molecular approaches (*1*, *2*). Animals engineered to express human genes linked to Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease have already provided valuable mechanistic insights into the pathogenesis of these dreaded diseases and are presenting exciting treatment possibilities for patients (*3*). Two recent papers now report on the first PD animal models in the fly and the mouse, which have some but not all of the cardinal features of PD. Masliah *et al.* (*4*) describe transgenic mice that overexpress human wild-type α-synuclein, whereas Feany and Bender (*5*) have engineered transgenic fruit flies to overexpress either wild-type human α-synuclein or a form of the protein that carries the PD mutations A53T (substitution of alanine at position 53 by threonine) or A30P (substitution of alanine at position 30 by proline).

PD is a movement disorder characterized by rigidity, tremor, slowed movement, and impaired gait and in some cases by impaired memory and cognitive dysfunction (*6*). The hallmark pathological feature is the progressive degeneration of dopamine neurons in an area of the brain called the substantia nigra pars compacta. An estimated 60 to 80% of dopamine neurons are lost before characteristic clinical signs of PD become manifest (*7*). Accompanying neuronal loss is the formation of inclusions in the cytoplasm of neuronal cell bodies (Lewy bodies) or in the extensions of neurons (Lewy neurites). These are spherical, dense cytoplasmic inclusions with a pale halo (first described by Lewy in 1912) that contain predominantly α-synuclein but also ubiquitin and other proteins (*6*, *7*). Lewy bodies are found in other neurodegenerative disorders but generally are considered to be a defining pathological feature of PD in conjunction with loss of dopamine neurons (*8*).

The PD model in the fruit fly developed by Feany and Bender (*5*) reproduces many features of the human disease. Expression of the human gene encoding wild-type α-synuclein or transgenes engineered to carry the A53T or A30P mutations results in an age-dependent loss of dopamine neurons in the fly, starting at mid-life. The loss of dopamine neurons is restricted to the nervous system and not all dopamine neurons are lost, reminiscent of the human disease in which dopamine neurons in the substantia nigra die, but those in the ventral tegmental area are spared. Structural analysis reveals neuronal cytoplasmic inclusions that have a dense core with radiating filaments and a halo reminiscent of Lewy bodies in humans. This pathology is not seen in normal aged flies. The flies express a progressive, age-dependent loss of motor function as measured by climbing activity in all three lines of transgenic flies, but loss of climbing activity



A comparison of animal models of PD. Recent molecular advances have enabled the engineering of mice and flies that carry wild-type or mutant versions of the protein α-synuclein, which is implicated in PD. A comparison of the features of the fly and mouse animal models of PD and how they correlate with the characteristics of the disease in human patients is shown.

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is more severe in flies expressing the A30P α-synuclein mutation. The significant decrease in motor activity in the A30P mutant is intriguing and may reflect a more aggressive disease, although altered transgenic expression could account for the difference. These transgenic flies recapitulate several cardinal features of human PD, including age-dependent onset, chronic progressive selective loss of dopamine neurons followed by loss of motor control, and development of Lewy body–like pathology (see the table).

Masliah and colleagues (*4*) engineered their mice to overexpress human wild-type α-synuclein driven by the platelet-derived growth factor promoter, which resulted in expression of α-synuclein in all neurons. The enzyme tyrosine hydroxylase (which is required for the synthesis of dopamine) was used as a marker for dopamine neurons and dopaminergic function. At 12 months of age, there is decreased expression of tyrosine hydroxylase protein and decreased activity of the enzyme in mice expressing the most α-synuclein. In addition, there is a decrease in the number of tyrosine hydroxylase–positive nerve terminals in the striatum, an area that receives projections from nigral dopamine neurons. Cytoplasmic inclusions containing α-synuclein and some containing ubiquitin are also observed. Additionally, the α-synuclein transgenic mice have impaired motor performance on the rotorod test (in which animals must balance on a rotating bar).

These mice demonstrate that overexpression of α-synuclein can injure dopamine neurons, induce formation of inclusions, and result in motor deficits. However, some cardinal features of PD have yet to be observed in these mice. There is no loss of dopamine neurons and the inclusions do not contain fibrils characteristic of Lewy bodies. This may be due to the age of the animals. Examining older mice may reveal loss of dopamine neurons with more characteristic Lewy body–like inclusions. Inclusions are also observed in the nuclei of neurons in the transgenic mice, which is not a feature of PD (see the table). Future studies will determine whether the decrease in motor performance is due to dopaminergic deficits or as yet unappreciated deficiencies in other motor areas. The Masliah *et al.* study is the first report of a genetically engineered mouse carrying a gene implicated in PD. Mice carrying the mutations associated with familial PD are sure to follow shortly. Building on the experience of expressing normal α-synuclein, taking cues from the fly model, and examining other lines of mice carrying the different familial mutations should enable the construction of a mouse model that recapitulates most, if not all, of the features of PD.

The initial characterization of these transgenic animals reveals that overexpression of wild-type and mutant α-synuclein induces neuropathological deficits with accompanying behavioral abnormalities. Are other features of PD also reproduced? It will be important to determine whether the neuronal injury in the mouse is confined to the dopaminergic system and whether dopamine neurons eventually die in the transgenic animals. Future work will determine whether there are decrements in the enzymes of mitochondrial complex 1 or increases in oxidative stress, which are features of the sporadic form of PD that affects the majority (>95%) of patients (*5*). However, the fly and mouse models provide us with a way to understand how overexpression of wild-type or mutant α-synuclein results in dopamine cell loss and neurological dysfunction.

Now that several genes have been linked to familial PD and the first animal models have been developed, a new era in PD research has begun. The power of fly genetics will allow identification of modifier and suppressor genes and other pharmacological and genetic manipulations that will help us to understand the signaling pathways that are critical for selective degeneration of dopamine neurons. The near future will see the generation of additional lines of mutant α-synuclein transgenic mice (in fact, α-synuclein A30P mutant transgenic mice have recently been reported); engineering mice that overexpress other PD-associated genes or that do not express them at all will soon follow. These animals will grant insight into selective dopamine neurodegeneration and should provide small-animal models to screen for new therapies that might affect the onset and progression of the more common (sporadic) form of PD.

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PERSPECTIVES: STRUCTURAL BIOLOGY

Light at the End of the Channel

Joan Weliky Conaway and Ronald C. Conaway

At the heart of bacterial and eukaryotic gene expression are the multisubunit RNA polymerases (RNAPs), industrious enzymes that catalyze the synthesis of RNA from a DNA template. Biochemical studies have provided a working model of how RNAPs move along the DNA template and catalyze the elongation of RNA, and they have revealed remarkable features of these macromolecular machines (*1, 2*). Unlike their kindred DNA polymerases, RNAPs are highly processive—that is, they are capable of synthesizing RNAs thousands and even millions of bases long without dissociating from the DNA template. The processivity of RNAPs is attributable, at least in part, to their ability to bind with exceptional tenacity to DNA and the growing RNA transcript. But despite the advantage of processivity, RNAPs synthesize RNA in fits and starts, pausing for varying lengths of time at each step of nucleotide addition and, at times, falling into an arrested state that can be reversed only by elongation factors, such as SII, GreA, or GreB. Pausing and arrest appear to result from backsliding of the polymerase along both the DNA and RNA, causing the growing end of the transcript to be displaced from the catalytic site, in a process that is either spontaneously reversible (in the case of pausing) or not (in the case of arrest).

Of the multisubunit RNAPs, eukaryotic RNA polymerase II (Pol II)—the enzyme that catalyzes synthesis of messenger RNA (mRNA)—is arguably king. With its 12 distinct protein subunits, Pol II carries out intricately regulated transcription and, in so doing, is the direct target of a diverse collection of transcription factors that control its activity at the preinitiation, initiation, and elongation stages of transcription. Despite the successful identification of many of these transcription factors, how they interact with their binding sites on the surface of Pol II and control its activity has remained a mystery, in large part because of a lack of high-resolution information about the structure of Pol II. Its large size, structural complexity, low abundance in cells, and fragility have rendered Pol II

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